REMARKS

Applicant respectfully requests reconsideration.

Claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142 and 144-146 were previously pending in this application. No claims have been amended or cancelled.

No new matter has been added.

Double Patenting Rejection

Claims 1, 5-9, 12, 15-18, 22, 129, 135-137 and 139-142 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 5 and 9-14 of copending Application No. 10/300,247.

Applicant notes the provisional rejection but defers substantive rebuttal until the cited application is allowed. MPEP 804(I)(B) states that "the merits of such a provisional rejection *can* be addressed by both the applicant and the examiner without waiting for the first patent to issue" (emphasis added). Notably, the MPEP does not require that the merits *must* be addressed in such a situation. Moreover, the MPEP also states that "the 'provisional' double patent rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that 'provisional' double patenting rejection is the only rejection remaining ...". Id. At that point, the examiner must withdraw the provisional rejection and allow the claims. Consistent with this practice, Applicant defers substantive rebuttal of the provisional rejections until the cited co-pending application is allowed.

Rejections under 35 U.S.C. §103

Claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142 and 144-146 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. 6,239,116 (Krieg et al.) in view of US 6,426,334 (Agrawal et al.), US 6,042,838 (Briles et al.), US 6,689,757 (Craig), Kincy-Cain et al. (Infection and Immunity, 1996, 64:1437-1440) and US 6,749,856 (Berzofsky et al.). Applicant respectfully traverses.

The rejected claims recite administration of a CpG oligonucleotide to a subject in need of a mucosal immune response for the purpose of inducing a mucosal immune response. The cited art

fails to teach and it does not render obvious that CpG oligonucleotides, when administered by mucosal routes, induce a mucosal immune response. In keeping with this lack of teaching and appreciation, the cited art therefore also does not teach and it does not render obvious CpG administration to subjects in need of a mucosal immune response.

The Examiner states that Krieg et al. and Agrawal et al. both teach "a method of inducing a mucosal immune response in a subject". Applicant strongly disagrees. Neither Krieg et al. nor Agrawal et al. teaches mucosal immune response induction in subjects having been administered CpG oligonucleotides. The Examiner does not identify where in either of these references such a teaching can be found. Instead the Examiner infers that the IL-12 immune response reported by Agrawal et al. is a mucosal immune response, citing the teachings of Kincy-Cain et al. and Berzofsky et al. The Examiner further argues that it would have been obvious to substitute the oral administration route of Krieg et al. with the intranasal or rectal administration routes taught by Agrawal et al. because of "the predictable result of inducing mucosal immunity".

The rejection is flawed both scientifically and legally. First, the Examiner incorrectly equates the IL-12 immune responses reported by Agrawal et al. with mucosal immune responses. The Examiner cites Kincy-Cain et al. and Berzofsky et al. in support of this assertion. However, neither of these references teach that an IL-12 immune response is a mucosal immune response. Kincy-Cain et al. states that IL-12 can augment a mucosal immune response that arises after administration of intracellular pathogen S. dublin. The reference provides no data that evidence a relationship between IL-12 and mucosal immune response induction. Instead it infers effects of systemically administered IL-12 on mucosal immunity based on overall survival of the experimental subjects. The reference further speculates that IL-12 "most probably" exerts its effects through non-antigen-specific mechanisms including through IFN-gamma production by innate immune cells such as NK cells. Berzofsky et al. reports that mucosal CTL immune responses are generated by administration to mucosal surfaces of soluble antigens or nucleic acids encoding such antigens. The reference does not teach that IL-12 must also be present in order to generate such mucosal immune responses although it contemplates administration of IL-12 presumably in order to augment a pre-existing mucosal immune response.

Other references evidence that mucosal immune responses, as indicated by the presence of mucosal IgA, can exist in the absence of IL-12 and conversely that mucosal immune responses do not necessarily result from the presence of IL-12. Simmons et al. (J. Immunol. 2002, 168:1804-1812, provided herewith) reports that IL-12 knockout (IL-12p40$^{-/-}$) mice mount gut-associated IgA responses after infection with C. rodentium (see for example Figure 6). The reference concludes that gut-associated IgA responses are not defective in IL-12 deficient mice. Arulanandam et al. (Vaccine 1999, 17:252-260, provided herewith) reports no change in lung IgA levels and suppressed fecal IgA levels in mice immunized intranasally with DNP-OVA with cholera toxin B subunit and IL-12. The reference therefore shows that IL-12 presence does not positively correlate with mucosal IgA levels. Marinaro et al. (J. Immunol. 1999, 162:114-121, provided herewith) documents that intranasal administration of IL-12 did not affect mucosal secretory IgA responses to oral or nasal vaccines. This reference too shows that IL-12 presence is not determinative of a mucosal immune response. Grdic et al. (Eur. J. Immunol., 1999, 29:1774-1784) compare the immunologic effects of cholera toxin (CT) and ISCOMs and report that while CT is an efficient inducer of a mucosal IgA response it did not induce detectable IL-12 at the protein and mRNA level. Conversely, the reference showed that although ISCOMs induced detectable IL-12 at the protein and mRNA level, it only poorly stimulated mucosal IgA production. Moreover, the reference reported that mucosal adjuvanticity of CT was unaffected in IL-12 knockout mice. It further concluded that "the immunomodulating ability of CT is independent of IL-12". These references refute the Examiner's position that an IL-12 immune response is equivalent to a mucosal immune response. Accordingly, there is no scientific basis for concluding that the immune responses of Agrawal et al. are mucosal immune responses.

These references also refute that the IL-12 immune responses reported by Agrawal et al. are inherently mucosal immune responses should the Examiner be taking this position. Inherency, in this instance, requires that a mucosal immune response necessarily and inevitably result each and every time IL-12 is present. In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)("Inherency ... may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."); Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 67 USPQ2d 1664 (Fed. Cir. 2003). The references provided by

Applicant clearly show this not to be the case. As a result, there is no evidence that the IL-12 immune responses of Agrawal et al. are inherently mucosal immune responses. Agrawal et al. and Krieg et al. do not teach mucosal immune responses following CpG oligonucleotide administration, either explicitly or inherently.

In the absence of any teaching in either Krieg et al. or Agrawal et al. of a mucosal immune response, there is no evidence that such an immune response would be predictable, as indicated by the Examiner. There was no appreciation by either Krieg et al. or Agrawal et al. that CpG oligonucleotides could stimulate a mucosal immune response. In the absence of such an appreciation (or, in other words, knowledge), there can be no predictability. And in the absence of such knowledge, there cannot be obviousness, as obviousness is premised on what is known in the art. In re Kuehl, 475 F.2d 658 (CCPA 1973); In re Rijckaert, 9 F.3d 1531, 1533-34 (Fed. Cir. 1993)("Obviousness cannot be predicated on what is unknown.").

The combination of Krieg et al. and Agrawal et al. does not yield methods for inducing mucosal immune responses by administering to subjects in need thereof a CpG oligonucleotide. The remaining references do not cure this deficiency, as argued in the previous response, to which the Examiner is referred. In particular, Craig does not cure this deficiency. As argued previously, Craig teaches away from the rejected claims because Craig requires delivery of a nucleic acid that encodes an epitope (or antigen) while the rejected claims explicitly exclude such a limitation. The Examiner counters that Craig is cited solely for the teaching of B-7 as a costimulatory molecule. Respectfully, the reference must be considered as a whole (i.e., in its entirety), including any disclosures that teach away from the rejected claims. MPEP 2141.03(VI); W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert denied, 469 U.S. 851 (1984). The teaching in Craig of administration of a nucleic acid that encodes an epitope is not merely an alternative contemplated by Craig; it is a necessary feature of the teachings of Craig as a whole and as such cannot simply be disregarded by the Examiner. Importantly, it is a teaching that discourages a common limitation of the rejected claims, and thus it is therefore relevant to the issue of obviousness. In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). Notwithstanding the deficiencies of Krieg et al. and Agrawal et al., the combination of these references with Craig yields a method that requires a limitation that is explicitly excluded from the

rejected claims. Thus, additionally, the combination does not yield each and every limitation of the rejected claims.

For at least these reasons, the combination of references does not render obvious the rejected claims. Reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated:

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Respectfully submitted,

By _____

Maria A. Trevisan, Reg. No. 48,207
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000